HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Cancer. 2020 March 01; 126(5): 958–970. doi:10.1002/cncr.32618.

Magnitude of Second Contralateral Breast Cancer Risk Reduction with Bilateral Mastectomy in Breast Cancer Patients: Data from California, 1998-2015

Allison W. Kurian, M.D., M.Sc.[1,2], **Alison J. Canchola, M.S.**[3], **Cindy S. Ma, B.S.**[1], **Christina A. Clarke, Ph.D.**[2,4], **Scarlett L. Gomez, Ph.D.**[3]

[1]Department of Medicine, Stanford University School of Medicine, Stanford, CA

[2]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA

[3]Department of Epidemiology and Biostatistics and Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco

[4]GRAIL, Menlo Park, CA

Abstract

Background: Increasingly, breast cancer patients undergo bilateral mastectomy (BLM). The magnitude of benefit is unknown.

Methods: We used SEER data on all women diagnosed in California from 1998-2015 with stage 0-III unilateral breast cancer and treated with BLM versus breast conserving therapy including surgery and radiation (BCT) or unilateral mastectomy (ULM). We measured relative risks of second contralateral breast cancer (CBC) and breast cancer death using Fine and Gray multivariable regression modeling adjusted for the competing risk of death and death from another cause, respectively, and potential confounding factors. We measured absolute excess risk (AERs) of CBC as the observed minus expected number of breast cancers in the general population, divided by 10,000 person-years at risk.

Results: Among 245,418 patients with median follow-up of 6.7 years, 7,784 (3.2%) developed CBC. Relative risks were lower after BLM (hazard ratio (HR) 0.10, 95% confidence interval 0.07-0.14) and higher after ULM (HR 1.07, 1.02-1.13) versus BCT. AERs were higher after BCT and ULM (5.0 and 13.6 more cases, respectively) than BLM (28.6 fewer cases). BLM reduced risk more for older women (38.0 fewer cases for age≥50, versus 17.9 among age<50) but provided similar risk reduction across categories of grade and tumor hormone receptor status. Compared to BCT, risk of breast cancer death was equivalent after BLM (HR 1.03, 0.96-1.11) and higher after ULM (HR 1.21, 1.17-1.25).

Address Correspondence to: Allison W. Kurian, M.D., M.Sc., Associate Professor of Medicine and of Health Research & Policy, Stanford University School of Medicine, HRP Redwood Building, Room T254A, 150 Governor's Lane, Stanford, CA 94305-5405, Telephone: 650-724-7375; Fax: 650-725-6951; akurian@stanford.edu.

Author Contributions:

Allison W. Kurian: Conceptualization, results analysis and interpretation, writing – original draft and writing – review and editing.
Alison J. Canchola: Formal data analysis, methodology and writing – review and editing
Cindy S. Ma: Results interpretation and writing – original draft
Christina A. Clarke: Conceptualization, data curation, results analysis and interpretation, and writing – review and editing
Scarlett L. Gomez: Conceptualization, data curation, results analysis and interpretation, and writing – review and editing

Conclusions: BLM may reduce second breast cancer risk by 34-43 cases per 10,000 person-years compared to other surgical procedures but is not associated with lower risk of death. Second breast cancers are rare, and their reduction should be weighed against harms associated with BLM.

Precis (Condensed Abstract):

Data from the population-based California Cancer Registry were used to estimate the magnitude of benefit from bilateral mastectomy among 245,418 breast cancer patients: compared to other surgical treatments, bilateral mastectomy reduces second contralateral breast cancer risk by 34-43 cases per 10,000 person-years. However, second breast cancers are rare and their prevention should be weighed against the harms associated with bilateral mastectomy.

Keywords

breast cancer; second contralateral breast cancer; bilateral mastectomy; cancer prevention; absolute excess risk

INTRODUCTION

The use of bilateral mastectomy (BLM) as a primary treatment for unilateral breast cancer has risen in the United States (U.S.) population, even though several clinical trials and observational studies demonstrate no survival benefit from this invasive procedure.[1-3] BLM is uncommon outside of the U.S. Moreover, BLM has greater morbidity than unilateral mastectomy (ULM) or breast conserving surgery with radiation (breast conserving therapy, BCT), in terms of complications, body image, recovery time and impact on employment.[4-8]

The choice to undergo BLM is complex. Although the probability of developing a contralateral, second breast cancer has declined in the U.S. over time[9], potentially due to more widespread use of adjuvant endocrine therapy[10], most patients report that fear of a subsequent breast cancer was their primary motivation for choosing BLM.[11] Prior studies have reported that BLM confers a relative risk reduction in range of 90-95% for second contralateral breast cancers among patients with a personal and family history of breast cancer.[12-15] However, there is no population-based evidence regarding the absolute reduction in second contralateral breast cancer risk conferred by BLM, particularly in patient subgroups defined by specific demographic and tumor characteristics. A better understanding of the effectiveness and absolute risk reduction from BLM across patient subgroups may guide shared decision-making among women with breast cancer and their surgeons.

Leveraging the large, diverse population of California, we used data from the population-based California Cancer Registry (CCR) to estimate: the risks of second contralateral breast cancers, risks of breast cancer-specific death, and absolute excess risks (relative to the general population) among women with stage 0-III breast cancer treated with BLM versus other surgical procedures from 1998-2015.

METHODS

The study population comprised all women residing in California when diagnosed with a first primary breast cancer (International Classification of Disease for Oncology, third edition, site codes C.50.0-50.9; histologic codes: 8000, 8010, 8020, 8022, 8050, 8140, 8201-8230, 8255, 8260, 8401, 8453, 8480-8525, and 8575) of American Joint Committee on Cancer (AJCC) stages 0-III between January 1, 1998 (study start date) and December 31, 2015 (study end date). Human subjects approval was covered under the Greater Bay Area Cancer Registry protocol approved by the Institutional Review Boards of the Cancer Prevention Institute of California and the University of California, San Francisco.

Information from the CCR included demographic and clinical characteristics, tumor features, initial treatment course, occurrence of a subsequent ipsilateral or contralateral breast cancer, vital status and cause of death as of December 31, 2015. Patients with subsequent ipsilateral cancers after more than six months were censored at the time of that event, as it is possible that these were in-breast tumor recurrences rather than second primary breast cancers. Only contralateral breast cancers (invasive or in-situ) were categorized as second breast cancers for the purpose of this analysis. To focus primarily on sequential rather than concurrent breast tumors, we excluded second breast tumors that were diagnosed less than six months after the first breast cancer diagnosis. In addition, we excluded women whose surgery occurred over six months after the initial diagnosis. Second tumors reported in the first six months after the initial diagnosis may have been diagnosed before the treatment surgery or may represent incidental diagnoses made on review of surgical pathology rather than true primaries. Surgeries more than 6 months after the initial diagnosis may reflect disease progression or recurrence, not treatment of the primary tumor. Patients were eligible for inclusion in the study if they had received one of four surgical treatments consistent with clinical practice guidelines within 6 months of the initial diagnosis: bilateral mastectomy (BLM), unilateral mastectomy (ULM), breast conserving treatment consisting of breast conserving surgery (BCS) with radiation (BCT),[16] and in women of age ≥70 years with stage I, hormone receptor-positive and HER2-negative breast cancer, BCS without radiation was also included as this treatment is consistent with practice guidelines for such patients.[16] Women who received non guideline-concordant surgical treatment were excluded from the analysis as they were considered non-representative of the standard of care. Neighborhood socioeconomic status (nSES) was measured by patients' residential census block group at diagnosis using an established multi-component scale.[17] Patient subgroups of fewer than five people are reported as n<5 to preserve patient anonymity, in accordance with practices of the CCR.[18] Tumors were considered estrogen receptor (ER) and progesterone receptor (PR)-negative if both receptors were negative. Tumors were considered ER and/or PR-positive if either receptor was positive.

We estimated associations with second contralateral breast cancer risk among patients undergoing BCT compared to those receiving other treatments using a Fine and Gray competing risk regression model, with follow-up beginning six months after the initial diagnosis. We selected Fine and Gray as the primary analytic method because it employs a multivariable model that reduces bias due to informative censoring. This method estimates the hazard rate ratio (HR) and 95% confidence intervals (CI) by modeling the hazard of the

cumulative incidence function while controlling for the competing risk of death and adjusting for the variables in Table 1 as potential confounders. We used Fine and Gray regression to estimate associations with the risk of breast cancer death, controlling for the competing risk of death from other causes, among patients undergoing BCT compared to those receiving other treatments,[19-21] and used Cox regression to estimate associations with risk of death from all causes.

The proportional hazards assumption was tested for all three outcomes using Cox regression by examining the correlation between time and scaled Schoenfeld residuals for surgical procedure and all covariates. The proportional hazards assumption was not violated for the subsequent contralateral breast cancer outcome, but was violated for the breast cancer-specific mortality outcome for stage, tumor size, grade, and ER/PR status and for all-cause mortality for age, stage, tumor size, lymph node involvement, grade and ER/PR status. When stage was included as an underlying stratifying variable in the Cox breast cancer-specific mortality model, additionally stratifying by tumor size and diagnosis year changed the HR for the main effect of surgical procedure somewhat, but additionally stratifying by tumor grade or by ER/PR status did not. Thus, stage (0, I, II, III), tumor size (<1.0, 1.0-1.9, 2.0-2.9, 3.0-4.9, >5.0 cm) and diagnosis year (1998-2003, 2004-2009, 2010-2015) were included as underlying stratifying variables in the fully adjusted Fine and Gray mortality models, which allowed the baseline hazard to vary by these factors, but tumor grade and ER/PR status were simply adjusted for in fully adjusted models. For all-cause mortality, age and stage were included as underlying stratification variables in the fully adjusted Cox regression model, and the other factors were simply adjusted for as stratifying by them did not change the main effect. Wald tests for interaction between surgical procedure and age, grade, and ER/PR status were computed using cross-product terms in models adjusted for all statistically significant ($p<0.05$) interactions with the stratification variable.

Based on evidence that absolute risk estimates are most easily understood and useful for patient decision-making[22,23], we calculated absolute excess risk (AER) of a second contralateral breast cancer as the number of observed breast cancer cases minus the expected number of incident breast cancers for the general California population. The expected number was calculated by multiplying age group- and calendar period-specific breast cancer incidence rates for California women by the corresponding person-years of follow-up in our cohort in jointly defined 5-year age groups and 3-year calendar periods and summing over all groups. The difference between the number of observed minus expected breast cancer cases was divided by person-years at risk (py). We presented AER estimates per 10,000 py.

All analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC) and all statistical tests were two-sided. $P<0.05$ was used to denote statistical significance and no adjustment was made for multiple comparisons.

RESULTS

A total of 421,643 women were diagnosed with a first primary breast cancer in California from 1998-2015. Patients were excluded from analysis hierarchically as follows: age at diagnosis <20 years (n=37); AJCC stage other than 0-III (n=35,057); diagnosis by death

certificate or autopsy only (n=43) or diagnosis not microscopically confirmed (n=278); ineligible histologic type (n=5,652); tumor size unknown (n=19,739), no tumor noted (n=445), microscopic (n=6,576), diffuse (n=854), Paget's disease (n<5) or mammographic diagnosis only (n=1,209); unknown nodal status (n=1,986); surgery other than ULM, BLM or BCT except among women age ≥70 years with stage I, ER/PR-positive and HER2-negative breast cancer (n=59,602 having lumpectomy without radiation and not meeting the age, stage, ER/PR and HER2 criteria above; n=8,912 no surgery, other surgery or not otherwise specified; and n=51 with unknown surgery); date of surgery >6 months after initial diagnosis (n=11,404); unknown surgery date (n=5,190); bilateral tumors at initial diagnosis (n=11); subsequent breast tumor <6 months after the first tumor (n=8,187); follow-up <6 months (n=10,991). After exclusions, 245,418 women remained, of whom 7,784 (3.2%) developed a contralateral second breast cancer more than 6 months after diagnosis of their first breast cancer. Median follow-up time was 6.7 years.

Of 245,418 women analyzed, 127,766 (52.1%) underwent BCT, 92,062 (37.5%) underwent ULM and 18,575 (7.6%) underwent BLM. There were 7,015 women (2.9%) of age ≥70 with stage I, ER/PR-positive, HER2-negative disease who received BCS without radiation. Most patients undergoing BCT were in stages 0-I (71.0%), compared to ULM (40.7%) and BLM (51.7%) (Table 1).

Compared to BCT recipients in a Fine and Gray multivariable-adjusted model (Table 2), BLM recipients had significantly lower risk of contralateral breast cancer (HR 0.10, 95% CI 0.07-0.14) while ULM recipients had higher risk (HR 1.07, 1.02-1.13) and BCS without radiation recipients (aged ≥70 with stage I, ER/PR-positive, HER2-negative disease) had equivalent risk (HR 0.91, 0.77-1.08). Results were similar in a model minimally adjusted for age and stage (BLM HR 0.10, 95% CI 0.07-0.13; ULM HR 1.10, 95% CI 1.05-1.15; BCS HR 0.85, 95% CI; 0.71-1.00). Stratified analyses in multivariable-adjusted models showed similar risk reductions associated with BLM in younger and older women (age <50: HR 0.09, 0.05-0.15, versus age ≥50: HR 0.11, 0.07-0.18; p-interaction for BLM=0.48) and by hormone receptor status (ER/PR-negative: HR 0.13, 0.07-0.23, versus ER/PR-positive: HR 0.09, 0.06-0.15; p-interaction for BCS=0.35), and greater risk reduction in those with lower grade (grade 1-2: HR 0.07, 0.04-0.13, versus grade 3: HR 0.14, 0.09-0.22; p-interaction for BLM=0.03). Supplemental Figure 1 shows unadjusted Cumulative Incidence Function plots for contralateral breast cancer development by surgical procedure stratified by age and hormone receptor status, which control for the competing risk of death.

AER of second contralateral breast cancer differed among surgical procedures (Table 3). BLM recipients had 28.6 fewer cases per 10,000 py compared to the general California population, while BCT recipients had 5.0 more cases and ULM recipients had 13.6 more cases. AER reduction after BLM was somewhat greater for women aged ≥50 years at initial diagnosis (38.0 fewer cases per 10,000 py) versus <50 years (17.9 fewer cases), with lower-grade (31.4 fewer cases) versus higher-grade tumors (23.9 fewer cases), and with ER/PR-positive (29.5 fewer cases) versus ER/PR-negative tumors (23.4 fewer cases). AER increases were notable in BCT recipients aged <50 (21.2 more cases per 10,000 py), with grade 3 (11.3 more cases) or ER/PR-negative tumors (19.2 more cases), with a similar pattern after ULM.

Compared to BCT recipients in a Fine and Gray multivariable-adjusted model (Table 4), BLM recipients had a similar risk of breast cancer death as BCT recipients (HR 1.03, CI 0.96-1.11). Risk of breast cancer death was slightly higher among ULM recipients (HR 1.21, 1.17-1.25) and recipients of BCS without radiation who were age ≥70 with stage I, ER/PR-positive, HER2-negative disease (1.36, 1.16-1.59). Risk of breast cancer death was statistically significantly associated with all factors included in the multivariable model (Table 4). Supplemental Figure 2 shows unadjusted Cumulative Incidence Function plots for breast cancer death by surgical procedure stratified by age and hormone receptor status, which control for the competing risk of death from other causes. Similarly for all-cause mortality, compared to BCT, risk was increased for ULM and BCS, but was similar for BLM (BLM HR 0.98, 95% CI 0.93-1.04; ULM HR 1.36, 95% CI 1.33-1.39; BCS HR 2.24, 95% CI 2.14-2.35).

DISCUSSION

We took advantage of the large, diverse, population-based California Cancer Registry to examine associations with second contralateral breast cancer and estimate the number of breast cancers potentially prevented by BLM. Among more than 240,000 patients diagnosed with unilateral breast cancer over a 18-year period, 3.2% developed a second contralateral breast cancer. The absolute excess risk reduction after BLM was 29 fewer cases of second contralateral breast cancer per 10,000 py, versus an excess risk of five more cases after BCT. This can be interpreted as an absolute difference of 34 fewer cases per 10,000 py at risk after BLM compared to BCT. Similarly, we estimated an excess risk of 14 more cases after ULM, or an absolute difference of 43 fewer cases per 10,000 py at risk after BLM compared to ULM. Notably, our results confirm those of several prior analyses[24-29], including our own[1], that found no improvement in the risk of death from breast cancer associated with BLM versus BCT. One possible explanation is that breast cancer survivors undergo more intensive secondary surveillance than before their diagnosis, and thus a second contralateral breast cancer is likely to be discovered at an earlier, more curable stage – and thus the risk of death from breast cancer is more likely to be determined by the first breast cancer diagnosis than by the second. Another possibility is unmeasured confounders in surgical treatment selection, which might result in patients with worse-prognosis tumors being more likely to receive BLM than BCT. Regardless of its cause, the repeatedly demonstrated absence of a survival benefit associated with BLM should be a crucial consideration in any discussion about BLM for secondary cancer prevention.

Importantly, our results join those of earlier studies in offering reassurance that second contralateral breast cancer is uncommon.[30] Previous studies have shown that second contralateral breast cancer incidence varies according to patient characteristics, with greater risk reported among younger women with ER/PR-negative tumors.[31-34] This likely reflects the higher prevalence of hereditary pathogenic variants in *BRCA1/2* and other DNA repair genes within this patient sub-population[33-36]; however, a recent study also reported a high risk of second contralateral breast cancers among women with a family history of breast cancer, even when genetic testing was negative.[37] Unlike survivors of ER/PR-positive cancers, ER/PR-negative survivors do not take adjuvant endocrine therapy that has the beneficial side effect of reducing their risk of a second breast cancer.[38] As in prior

studies[30,32-34,37], we found a significant increase in second breast cancer risk among women aged <50 years at initial diagnosis and/or with ER/PR-negative disease. These findings are consistent with clinical practice guidelines that advise genetic counseling and testing among women diagnosed at age <50 years or with triple-negative breast cancer.[39]

Our absolute excess risk estimates enable comparison of surgical options. For example, our AER estimate for ER/PR-negative survivors suggests 19 (for BCT) or 28 (for ULM) more second contralateral breast cancers per 10,000 py (compared to the population average), versus 23 fewer cases after BLM: this might be interpreted as 42 or 51 fewer second contralateral breast cancers after BLM compared to BCS or ULM. With ER/PR-positive disease, the difference is more modest, at 31 or 38 fewer second contralateral breast cancers after BLM compared to BCS or ULM. However, caution is needed in extrapolating aggregate data to individuals. Moreover, patients differ in numeracy and in the valence they place on risk estimates. What one patient might consider a negligible benefit of BLM, weighed against its potential harms of greater pain, recovery time, impact on body image and employment,[4-6] might seem worthwhile to another. These estimates can help benchmark the benefits of BLM according to patient characteristics.

Our study has some limitations. Most importantly, we cannot discount the possibility that the observed risk reductions may reflect confounding. We adjusted for available known confounders for contralateral breast cancer development and breast cancer death using a Fine and Gray multivariable regression model. However, we cannot exclude the influence of unmeasured confounders, particularly inherited cancer susceptibility. Since SEER does not routinely collect germline genetic testing information, we could not distinguish pathogenic variant carriers who might benefit most from BLM, and this is a limitation of the study. Ongoing efforts to link genetic testing data to SEER records should facilitate re-evaluation of this question in the future.[40,41] Another limitation is the relatively short median follow-up time of 6.7 years. Our study focused on women with first primary breast cancers but it is possible that these women differ from those who pursue BLM after diagnosed with a second or third primary breast cancer. Our AER estimates are based on a standardized incidence ratio approach that compares to breast cancer rates in the general population, which is an accepted way to derive such estimates[31,42] but are not adjusted for confounders other than age and calendar year, and differ from the Fine and Gray method we used elsewhere in this study. While the study sample size was very large, it is still possible that smaller, possibly important differences may not have been detected. $P<0.05$ was used to denote statistical significance and no adjustment was made for multiple comparisons; the chance of falsely rejecting a null hypothesis may exceed 0.05. The study is limited to California and may not fully represent other populations. However, the study's notable strengths include the size and diversity of California's population and a registry that is stringently audited for quality.

Implications for Patient Care

Among breast cancer patients, BLM is estimated to reduce the risk of developing a second contralateral breast cancer substantially compared to BCT or ULM, and to a level well below the average woman's risk of developing a first breast cancer. However, there is no evidence that BLM reduces the risk of death from breast cancer. Second contralateral breast

cancers are uncommon and the absolute risk reduction with BLM varies according to patient age and tumor characteristics. Absolute risk estimates are often more comprehensible to patients, and their presentation is recommended.[22,23] These results may be used to guide shared decision-making about the surgical prevention of second contralateral breast cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032Iawarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute, Cancer Registry of Greater California. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors. This project has been funded in part with Federal funds from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN261201800010I. Additional funding sources included the Suzanne Pride Bryan Fund for Breast Cancer Research, the Jan Weimer Faculty Chair in Breast Oncology, and the BRCA Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Clarke is currently employed by GRAIL, Inc., a life sciences company developing tests for early cancer detection, but does not report conflict of interest with the topic addressed by this analysis. Dr. Kurian has received research funding to her institution from Myriad Genetics for an unrelated project. The authors declare no conflicts of interest.

REFERENCES

1. Kurian AW, Lichtensztajn DY, Keegan TH, Nelson DO, Clarke CA, Gomez SL. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998-2011. JAMA. 2014;312(9):902–914. [PubMed: 25182099]
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233–1241. [PubMed: 12393820]
3. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25(33):5203–5209. [PubMed: 17954711]
4. Silva AK, Lapin B, Yao KA, Song DH, Sisco M. The Effect of Contralateral Prophylactic Mastectomy on Perioperative Complications in Women Undergoing Immediate Breast Reconstruction: A NSQIP Analysis. Ann Surg Oncol. 2015;22(11):3474–3480. [PubMed: 26001862]
5. Anderson C, Islam JY, Elizabeth Hodgson M, et al. Long-Term Satisfaction and Body Image After Contralateral Prophylactic Mastectomy. Ann Surg Oncol. 2017;24(6):1499–1506. [PubMed: 28058563]
6. Jagsi R, Abrahamse PH, Lee KL, et al. Treatment decisions and employment of breast cancer patients: Results of a population-based survey. Cancer. 2017;123(24):4791–4799. [PubMed: 28990155]
7. Hwang ES, Locklear TD, Rushing CN, et al. Patient-Reported Outcomes After Choice for Contralateral Prophylactic Mastectomy. J Clin Oncol. 2016;34(13):1518–1527. [PubMed: 26951322]

8. Parker PA, Peterson SK, Shen Y, et al. Prospective Study of Psychosocial Outcomes of Having Contralateral Prophylactic Mastectomy Among Women With Nonhereditary Breast Cancer. J Clin Oncol. 2018;36(25):2630–2638. [PubMed: 30044695]
9. Nichols HB, Berrington de Gonzalez A, Lacey JV Jr., Rosenberg PS, Anderson WF. Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. J Clin Oncol. 2011;29(12):1564–1569. [PubMed: 21402610]
10. Mariotto AB, Feuer EJ, Harlan LC, Abrams J. Dissemination of adjuvant multiagent chemotherapy and tamoxifen for breast cancer in the United States using estrogen receptor information: 1975-1999. J Natl Cancer Inst Monogr. 2006(36):7–15. [PubMed: 17032888]
11. Hawley ST, Jagsi R, Morrow M, et al. Social and Clinical Determinants of Contralateral Prophylactic Mastectomy. JAMA Surg. 2014;149(6):582–589. [PubMed: 24849045]
12. McDonnell SK, Schaid DJ, Myers JL, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol. 2001;19(19):3938–3943. [PubMed: 11579114]
13. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 2005;23(19):4275–4286. [PubMed: 15795415]
14. Goldflam K, Hunt KK, Gershenwald JE, et al. Contralateral prophylactic mastectomy. Predictors of significant histologic findings. Cancer. 2004;101(9):1977–1986. [PubMed: 15389473]
15. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg. 2000;180(6):439–445. [PubMed: 11182394]
16. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(3):310–320. [PubMed: 29523670]
17. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control. 2001;12(8):703–711. [PubMed: 11562110]
18. California Cancer Registry. http://www.ccrcal.org. Accessed March 14, 2019.
19. Calip GS, Law EH, Ko NY. Racial and ethnic differences in risk of second primary cancers among breast cancer survivors. Breast Cancer Res Treat. 2015;151(3):687–696. [PubMed: 26012645]
20. Canchola AJ, Horn-Ross PL, Purdie DM. Risk of second primary malignancies in women with papillary thyroid cancer. Am J Epidemiol. 2006;163(6):521–527. [PubMed: 16421240]
21. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ. 1987(82):1–407.
22. Emmons KM, Wong M, Puleo E, Weinstein N, Fletcher R, Colditz G. Tailored computer-based cancer risk communication: correcting colorectal cancer risk perception. J Health Commun. 2004;9(2):127–141. [PubMed: 15204824]
23. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1–37. [PubMed: 20346624]
24. Wong SM, Freedman RA, Sagara Y, Aydogan F, Barry WT, Golshan M. Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer. Ann Surg. 2017;265(3):581–589. [PubMed: 28169929]
25. Agarwal S, Pappas L, Agarwal J. Association between unilateral or bilateral mastectomy and breast cancer death in patients with unilateral ductal carcinoma. Cancer Manag Res. 2017;9:649–656. [PubMed: 29180900]
26. Pesce C, Liederbach E, Wang C, Lapin B, Winchester DJ, Yao K. Contralateral prophylactic mastectomy provides no survival benefit in young women with estrogen receptor-negative breast cancer. Ann Surg Oncol. 2014;21(10):3231–3239. [PubMed: 25081341]
27. Bouchard-Fortier A, Baxter NN, Sutradhar R, et al. Contralateral prophylactic mastectomy in young women with breast cancer: a population-based analysis of predictive factors and clinical impact. Curr Oncol. 2018;25(6):e562–e568. [PubMed: 30607124]

28. Yao K, Winchester DJ, Czechura T, Huo D. Contralateral prophylactic mastectomy and survival: report from the National Cancer Data Base, 1998-2002. Breast Cancer Res Treat. 2013;142(3): 465–476. [PubMed: 24218052]
29. Donovan CA, Bao J, Gangi A, et al. Bilateral Mastectomy as Overtreatment for Breast Cancer in Women Age Forty Years and Younger with Unilateral Operable Invasive Breast Cancer. Ann Surg Oncol. 2017;24(8):2168–2173. [PubMed: 28417238]
30. Bernstein JL, Lapinski RH, Thakore SS, Doucette JT, Thompson WD. The descriptive epidemiology of second primary breast cancer. Epidemiology. 2003;14(5):552–558. [PubMed: 14501270]
31. Kurian AW, McClure LA, John EM, Horn-Ross PL, Ford JM, Clarke CA. Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst. 2009;101(15):1058–1065. [PubMed: 19590058]
32. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst. 2010;102(6):401–409. [PubMed: 20185801]
33. Marmor S, Portschy PR, Burke EE, Virnig BA, Tuttle TM. Prognostic Factors for Metachronous Contralateral Breast Cancer: Implications for Management of the Contralateral Breast. Breast J. 2017;23(3):299–306. [PubMed: 27988977]
34. Reiner AS, Lynch CF, Sisti JS, et al. Hormone receptor status of a first primary breast cancer predicts contralateral breast cancer risk in the WECARE study population. Breast Cancer Res. 2017;19(1):83. [PubMed: 28724391]
35. John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA. 2007;298(24):2869–2876. [PubMed: 18159056]
36. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304–311. [PubMed: 25452441]
37. Reiner AS, Sisti J, John EM, et al. Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol. 2018;36(15):1513–1520. [PubMed: 29620998]
38. Goss PE, Ingle JN, Pritchard KI, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med. 2016;375(3):209–219. [PubMed: 27264120]
39. Daly MB, Pilarski R, Berry M, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017. J Natl Compr Canc Netw. 2017;15(1):9–20. [PubMed: 28040716]
40. Katz SJ, Ward KC, Hamilton AS, et al. Gaps in Receipt of Clinically Indicated Genetic Counseling After Diagnosis of Breast Cancer. J Clin Oncol. 2018;36(12):1218–1224. [PubMed: 29528794]
41. Kurian AW, Ward KC, Howlader N, et al. Genetic Testing and Results in Population-Based Breast and Ovarian Cancer Patients. Abstract presented at the American Society of Clinical Oncology Annual Meeting; June 1-5, 2018; Chicago, IL.
42. Engels EA, Pfeiffer RM, Fraumeni JF Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–1901. [PubMed: 22045767]

Table 1.

Patient and tumor characteristics among 245,418 breast cancer patients of stages 0-III, 1998-2015, California

	Surgical Procedures									
	Breast conserving surgery without radiation (in patients aged ≥70, stage I, ER/PR-positive, and HER2-negative)		Breast conserving therapy (surgery with radiation)		Unilateral mastectomy		Bilateral mastectomy		All Patients	
	N	Column %	N	Column %	N	Column %	N	Column %	N	Column %
All	7,015	100.0	127,766	100.0	92,062	100.0	18,575	100.0	245,418	100.0
Race/Ethnicity										
Non-Hispanic (NH) White	5,510	78.5	87,149	68.2	53,920	58.6	13,171	70.9	159,750	65.1
NH Black	311	4.4	6,964	5.5	5,271	5.7	721	3.9	13,267	5.4
Hispanic	698	10.0	18,448	14.4	17,196	18.7	2,662	14.3	39,004	15.9
Chinese	112	1.6	3,773	3.0	3,773	4.1	366	2.0	8,024	3.3
Japanese	111	1.6	1,774	1.4	1,367	1.5	172	0.9	3,424	1.4
Filipina	100	1.4	4,260	3.3	5,124	5.6	612	3.3	10,096	4.1
Other Asian/Pacific Islander	105	1.5	4,414	3.5	4,681	5.1	698	3.8	9,898	4.0
Other or unknown	68	1.0	984	0.8	730	0.8	173	0.9	1,955	0.8
Age at diagnosis, years										
<40	-	-	4,407	3.4	5,541	6.0	2,470	13.3	12,418	5.1
40-49	-	-	22,195	17.4	18,138	19.7	6,227	33.5	46,560	19.0
50-64	-	-	54,188	42.4	32,792	35.6	7,101	38.2	94,081	38.3
≥65	7,015	100.0	46,976	36.8	35,591	38.7	2,777	15.0	92,359	37.6
Marital status at diagnosis										
Unmarried	3,925	56.0	47,126	36.9	37,489	40.7	5,954	32.1	94,494	38.5
Married	2,838	40.5	77,404	60.6	52,012	56.5	12,173	65.5	144,427	58.8
Unknown	252	3.6	3,236	2.5	2,561	2.8	448	2.4	6,497	2.6
Neighborhood socioeconomic status (SES), quintiles										
First (lowest) quintile	675	9.6	11,561	9.0	12,638	13.7	1,313	7.1	26,187	10.7
Second quintile	1,156	16.5	19,109	15.0	17,164	18.6	2,467	13.3	39,896	16.3
Third quintile	1,479	21.1	25,536	20.0	19,445	21.1	3,480	18.7	49,940	20.3
Fourth quintile	1,754	25.0	31,676	24.8	21,199	23.0	4,717	25.4	59,346	24.2
Fifth (highest) quintile	1,951	27.8	39,884	31.2	21,616	23.5	6,598	35.5	70,049	28.5
Insurance status										
No insurance	17	0.2	798	0.6	799	0.9	123	0.7	1,737	0.7
Private only	2,111	30.1	81,644	63.9	53,931	58.6	14,549	78.3	152,235	62.0

	Surgical Procedures									
	Breast conserving surgery without radiation (in patients aged ≥70, stage I, ER/PR-positive, and HER2-negative)		Breast conserving therapy (surgery with radiation)		Unilateral mastectomy		Bilateral mastectomy		All Patients	
	N	Column %	N	Column %	N	Column %	N	Column %	N	Column %
Medicare with or without private	4,109	58.6	27,606	21.6	20,437	22.2	1,989	10.7	54,141	22.1
Any Medicaid, military or other public	707	10.1	13,283	10.4	15,045	16.3	1,605	8.6	30,640	12.5
Unknown	71	1.0	4,435	3.5	1,850	2.0	309	1.7	6,665	2.7
Stage										
0	-	-	19,545	15.3	9,436	10.2	3,022	16.3	32,003	13.0
I	7,015	100.0	71,106	55.7	28,044	30.5	6,570	35.4	112,735	45.9
II	-	-	33,906	26.5	40,242	43.7	6,578	35.4	80,726	32.9
III	-	-	3,209	2.5	14,340	15.6	2,405	12.9	19,954	8.1
Tumor size, centimeters										
<1	2,785	39.7	34,934	27.3	11,883	12.9	3,450	18.6	53,052	21.6
1.0-1.9	3,878	55.3	56,678	44.4	25,909	28.1	5,692	30.6	92,157	37.6
2.0-2.9	352	5.0	23,845	18.7	21,802	23.7	4,032	21.7	50,031	20.4
3.0-5.0	0	0.0	10,729	8.4	22,173	24.1	3,480	18.7	36,382	14.8
>5	0	0.0	1,580	1.2	10,295	11.2	1,921	10.3	13,796	5.6
Tumor grade										
Grade 1	3,195	45.5	32,781	25.7	14,553	15.8	3,142	16.9	53,671	21.9
Grade 2	3,047	43.4	53,449	41.8	36,893	40.1	7,555	40.7	100,944	41.1
Grade 3	554	7.9	36,376	28.5	35,575	38.6	6,981	37.6	79,486	32.4
Unknown	219	3.1	5,160	4.0	5,041	5.5	897	4.8	11,317	4.6
Tumor histology										
Ductal	5,758	82.1	110,403	86.4	78,103	84.8	15,500	83.4	209,764	85.5
Lobular	579	8.3	7,866	6.2	8,793	9.6	2,162	11.6	19,400	7.9
Other	678	9.7	9,497	7.4	5,166	5.6	913	4.9	16,254	6.6
Estrogen/ progesterone receptors (ER/PR)										
Both negative	-	-	15,923	12.5	16,025	17.4	2,956	15.9	34,904	14.2
Either positive	7,015	100.0	101,100	79.1	65,036	70.6	14,250	76.7	187,401	76.4
Unknown or borderline	-	-	10,743	8.4	11,001	11.9	1,369	7.4	23,113	9.4
HER2 status										
Negative	7,015	100.0	76,400	59.8	48,090	52.2	11,254	60.6	142,759	58.2
Positive	-	-	12,527	9.8	13,435	14.6	2,580	13.9	28,542	11.6
Unknown or borderline	-	-	38,839	30.4	30,537	33.2	4,741	25.5	74,117	30.2

	Surgical Procedures									
	Breast conserving surgery without radiation (in patients aged ≥70, stage I, ER/PR-positive, and HER2-negative)		Breast conserving therapy (surgery with radiation)		Unilateral mastectomy		Bilateral mastectomy		All Patients	
	N	Column %	N	Column %	N	Column %	N	Column %	N	Column %
Lymph node involvement										
Negative	-	-	105,130	82.3	54,443	59.1	12,234	65.9	178,777	72.8
Positive	-	-	22,636	17.7	37,619	40.9	6,341	34.1	66,641	27.2
Year of cancer diagnosis										
1998	8	0.1	5,781	4.5	5,691	6.2	252	1.4	11,732	4.8
1999	153	2.2	5,949	4.7	5,747	6.2	295	1.6	12,144	4.9
2000	185	2.6	6,535	5.1	5,834	6.3	375	2.0	12,929	5.3
2001	240	3.4	6,767	5.3	5,970	6.5	486	2.6	13,463	5.5
2002	257	3.7	7,088	5.5	5,739	6.2	507	2.7	13,591	5.5
2003	240	3.4	7,112	5.6	5,224	5.7	602	3.2	13,178	5.4
2004	272	3.9	7,364	5.8	5,369	5.8	724	3.9	13,729	5.6
2005	344	4.9	7,984	6.2	5,169	5.6	660	3.6	14,157	5.8
2006	447	6.4	7,671	6.0	5,199	5.6	830	4.5	14,147	5.8
2007	460	6.6	7,948	6.2	5,283	5.7	1,028	5.5	14,719	6.0
2008	466	6.6	7,837	6.1	5,371	5.8	1,223	6.6	14,897	6.1
2009	515	7.3	7,561	5.9	5,180	5.6	1,443	7.8	14,699	6.0
2010	482	6.9	7,749	6.1	5,199	5.6	1,574	8.5	15,004	6.1
2011	630	9.0	7,941	6.2	5,064	5.5	1,748	9.4	15,383	6.3
2012	626	8.9	7,660	6.0	4,987	5.4	1,856	10.0	15,129	6.2
2013	686	9.8	7,443	5.8	4,715	5.1	2,115	11.4	14,959	6.1
2014	692	9.9	7,421	5.8	4,166	4.5	1,930	10.4	14,209	5.8
2015	312	4.4	3,955	3.1	2,155	2.3	927	5.0	7,349	3.0
Reporting hospital was National Cancer Institute-designated cancer center										
No	6,734	96.0	120,670	94.4	87,958	95.5	17,284	93.0	232,646	94.8
Yes	281	4.0	7,096	5.6	4,104	4.5	1,291	7.0	12,772	5.2
SES of hospital's patient distribution										
Low: ≥50% lowest 2 quintiles, <50% highest 2	1,039	14.8	19,554	15.3	20,401	22.2	2,636	14.2	43,630	17.8
Medium: neither low nor high	2,102	30.0	36,918	28.9	29,909	32.5	4,812	25.9	73,741	30.0
High: ≥50% highest 2 quintiles, <50% lowest 2	3,871	55.2	71,275	55.8	41,744	45.3	11,124	59.9	128,014	52.2

	Surgical Procedures									
	Breast conserving surgery without radiation (in patients aged ≥70, stage I, ER/PR-positive, and HER2-negative)		Breast conserving therapy (surgery with radiation)		Unilateral mastectomy		Bilateral mastectomy		All Patients	
	N	Column %	N	Column %	N	Column %	N	Column %	N	Column %
<5 cancer patients at facility	<5		19	0.0	8	0.0	<5		33	0.0
Adjuvant chemotherapy										
No	6,939	98.9	90,238	70.6	54,318	59.0	10,255	55.2	161,750	65.9
Yes	76	1.1	37,528	29.4	37,744	41.0	8,320	44.8	83,668	34.1
Adjuvant radiation										
No	7,015	100.0	0	0.0	75,201	81.7	15,419	83.0	97,635	39.8
Yes	0	0.0	127,766	100.0	16,861	18.3	3,156	17.0	147,783	60.2
Breast cancer outcomes										
Subsequent contralateral breast cancer (BC)	143	2.0	4,213	3.3	3,384	3.7	44	0.2	7,784	3.2
Subsequent ipsilateral BC	88	1.3	2,387	1.9	310	0.3	93	0.5	2,878	1.2
Subsequent bilateral BC	0	0.0	<5		0	0.0	<5		<5	
Subsequent BC, laterality unknown	0	0.0	19	0.0	28	0.0	<5		51	0.0
Died of breast cancer	152	2.2	5,296	4.1	10,178	11.1	983	5.3	16,609	6.8
Died of other cause	1,905	27.2	12,346	9.7	13,519	14.7	575	3.1	28,345	11.5
Died of unknown cause	24	0.3	446	0.3	602	0.7	40	0.2	1,112	0.5
Lost to follow up before 12/31/2015 (study end)	538	7.7	10,090	7.9	8,987	9.8	1,474	7.9	21,089	8.6
Followed until 12/31/2015	4,165	59.4	92,968	72.8	55,054	59.8	15,361	82.7	167,548	68.3

Table 2.

Associations with risk of second contralateral breast cancer with 95% confidence intervals (CI) among breast cancer patients stages 0-III, 1998-2015, California*

	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Surgical procedure				
Breast conserving therapy: surgery with radiation (BCT, reference)	1.00	-	-	-
Breast conserving surgery without radiation (BCS): restricted to age ≥70, stage I, estrogen/ progesterone receptor (ER/PR)-positive and HER2-negative	0.91	0.77	1.08	0.30
Unilateral mastectomy (ULM)	1.07	1.02	1.13	0.0081
Bilateral mastectomy (BLM)	0.10	0.07	0.14	<0.0001
Race/ethnicity				
Non-Hispanic (NH) White (reference)	1.00	-	-	-
NH Black	1.23	1.13	1.35	<0.0001
Hispanic	1.00	0.94	1.07	0.97
Chinese	1.12	0.97	1.30	0.13
Japanese	1.00	0.81	1.22	0.97
Filipina	1.30	1.17	1.44	<0.0001
Other Asian/Pacific Islander ethnicity	1.02	0.90	1.16	0.77
Age at diagnosis, years				
<40	1.16	1.05	1.29	0.0034
40-49	0.96	0.91	1.02	0.20
50-64 (reference)	1.00	-	-	-
≥65	0.90	0.84	0.96	0.0024
Marital status at diagnosis				
Married (reference)	1.00	-	-	-
Unmarried	1.01	0.96	1.06	0.71
Neighborhood socioeconomic status (SES), quintiles				
First (lowest) quintile (reference)	1.00	-	-	-
Second quintile	0.94	0.85	1.04	0.23
Third quintile	0.93	0.84	1.02	0.14
Fourth quintile	1.00	0.91	1.10	0.99
Fifth (highest) quintile	0.97	0.88	1.06	0.48
Insurance status				
Private only (reference)	1.00	-	-	-
No insurance	1.08	0.85	1.36	0.54
Medicare with or without private	0.98	0.91	1.04	0.46
Any Medicaid, military or other public	0.92	0.85	1.00	0.06
Stage				
0	1.41	1.29	1.54	<0.0001
I (reference)	1.00	-	-	-
II	0.92	0.86	0.98	0.02
III	0.99	0.88	1.11	0.81

	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Tumor size (per centimeter increase)	1.01	1.00	1.02	0.06
Tumor grade				
Grade 1 (reference)	1.00	-	-	-
Grade 2	0.97	0.91	1.02	0.23
Grade 3	0.93	0.86	0.99	0.04
Tumor histology				
Ductal (reference)	1.00	-	-	-
Lobular	1.00	0.91	1.10	0.94
Other	0.99	0.91	1.07	0.75
Estrogen/progesterone receptors (ER/PR)				
Either positive (reference)	1.00	-	-	-
Both negative	1.30	1.21	1.39	<0.0001
Lymph node involvement				
Negative (reference)	1.00	-	-	-
Positive	0.94	0.88	1.02	0.14
Year of diagnosis (per 1-year increase)	0.97	0.97	0.98	<0.0001
Reporting hospital National Cancer Institute-designated cancer center				
No (reference)	1.00	-	-	-
Yes	0.98	0.85	1.12	0.72
SES of hospital's patient distribution				
High: ≥50% highest 2 quintiles, <50% lowest 2 (reference)	1.00	-	-	-
Low: ≥50% lowest 2 quintiles, <50% highest 2	0.99	0.91	1.07	0.73
Medium: neither low nor high	0.98	0.92	1.04	0.45
Adjuvant therapy (chemotherapy and/or radiation)				
No (reference)	1.00	-	-	-
Yes	0.93	0.88	0.99	0.03
Stratified Models				
Surgical procedures by age category at diagnosis **				
Age <50 years				
BCT (reference)	1.00	-	-	-
ULM	0.99	0.89	1.09	0.77
BLM	0.09	0.05	0.15	<0.0001
Age ≥50 years				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	0.88	0.74	1.04	0.14
BCT (reference)	1.00	-	-	-
ULM	1.11	1.05	1.18	0.0003
BLM	0.11	0.07	0.18	<0.0001
Surgical procedures by grade categories †				
Grade 1 or 2				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	0.86	0.71	1.05	0.13
BCT (reference)	1.00	-	-	-

	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
ULM	1.10	1.03	1.18	0.003
BLM	0.07	0.04	0.13	<0.0001
Grade 3				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	1.10	0.63	1.91	0.73
BCT (reference)	1.00	-	-	-
ULM	1.02	0.93	1.10	0.72
BLM	0.14	0.09	0.22	<0.0001
Surgical procedures by ER/PR categories[‡]				
ER/PR-negative				
BCT (reference)	1.00	-	-	-
ULM	1.02	0.90	1.15	0.78
BLM	0.13	0.07	0.23	<0.0001
ER/PR-positive				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	0.92	0.77	1.09	0.34
BCT (reference)	1.00	-	-	-
ULM	1.11	1.04	1.18	0.002
BLM	0.09	0.06	0.15	<0.0001

[*] Fine and Gray regression model with death as a competing risk, adjusted for the variables in the table.

[**] P interaction=0.09 for the global test of an interaction between age and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with age (race, insurance type, stage, hormone receptor status, diagnosis year, and adjuvant treatment). Individual interaction terms were p=0.03 for ULM and p=0.48 for BLM

[†] P-interaction=0.06 for the global test of an interaction between grade and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with grade (race and lymph node involvement). Individual interaction terms were p=0.57 for BCS, p=0.20 for ULM, and p=0.03 for BLM

[‡] P-interaction=0.15 for the global test of an interaction between ER/PR status and surgical procedure from a fully adjusted model additionally adjusted for statistically significant interactions with ER/PR status (race and stage). Individual interaction terms were p=0.11 for ULM and p=0.35 for BLM

Table 3.

Absolute excess risk of second contralateral breast cancer, shown as excess cases per 10,000 person-years among breast cancer patients of stages 0-III relative to the general population, 1998-2015, California*

	Observed	Expected	Person-years, total	Absolute Excess Risk
Surgical procedure				
Breast conserving surgery without radiation (BCS): restricted to age ≥70, stage I, estrogen/progesterone receptor (ER/PR)-positive and HER2-negative	143	145	32,384	−0.7
Breast-conserving therapy: surgery with radiation (BCT)	4,213	3,755	918,682	5.0
Unilateral mastectomy (ULM)	3,384	2,517	639,370	13.6
Bilateral mastectomy (BLM)	44	327	99,017	−28.6
Age at first breast cancer diagnosis, years				
<50	1,905	1,066	436,687	19.2
≥50	5,879	5,678	1,252,767	1.6
Tumor grade				
1 or 2	4,675	4,349	1,059,270	3.1
3	2,641	1,999	534,040	12.0
Estrogen and progesterone receptors (ER/PR)				
Both negative	1,320	858	228,891	20.2
Either positive	5,229	4,979	1,236,805	2.0
Surgical procedures by age category at diagnosis				
Age <50 years				
BCT	976	531	210,551	21.2
ULM	911	435	179,820	26.5
BLM	18	101	46,315	−17.9
Age ≥50 years				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	143	145	32,384	−0.7
BCT	3,237	3,224	708,131	0.2
ULM	2,473	2,082	459,550	8.5
BLM	26	226	52,702	−38.0
Surgical procedures by grade categories				
Grade 1 or 2				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	121	128	28,568	−2.5
BCT	2,706	2,570	614,130	2.2
ULM	1,832	1,456	359,800	10.4
BLM	16	194	56,772	−31.4
Grade 3				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	13	12	2,556	5.8
BCT	1,285	993	258,663	11.3
ULM	1,319	886	237,151	18.3
BLM	24	109	35,670	−23.9
Surgical procedures by ER/PR categories				
ER/PR-negative				

	Observed	Expected	Person-years, total	Absolute Excess Risk
BCT	649	431	113,063	19.2
ULM	660	381	101,009	27.7
BLM	11	46	14,819	−23.4
ER/PR-positive				
BCS: age ≥70, stage I, ER/PR-positive, HER2-negative	143	145	32,384	−0.7
BCT	2,950	2,871	696,214	1.1
ULM	2,109	1,723	435,820	8.9
BLM	27	240	72,387	−29.5

* Age- and calendar period-adjusted

Table 4.

Associations with risk of breast cancer death with 95% confidence intervals (CI) among breast cancer patients stages 0-III, 1998-2015, California*

	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Surgical procedure				
Breast conserving therapy with radiation (reference)	1.00	-	-	-
Breast conserving surgery without radiation: restricted to age ≥70, stage I, estrogen/progesterone receptor (ER/PR)-positive and HER2-negative	1.36	1.16	1.59	0.0001
Unilateral mastectomy	1.21	1.17	1.25	<0.0001
Bilateral mastectomy	1.03	0.96	1.11	0.35
Age at first breast cancer diagnosis, years				
<40 (reference)	1.00	-	-	-
40-49	0.78	0.73	0.83	<0.0001
50-64	0.79	0.74	0.84	<0.0001
≥65	0.93	0.87	0.99	0.03
Race/ethnicity				
Non-Hispanic (NH) White (reference)	1.00	-	-	-
NH Black	1.21	1.14	1.28	<0.0001
Hispanic	0.92	0.88	0.96	0.0004
Chinese	0.84	0.75	0.93	0.0006
Japanese	0.81	0.69	0.94	0.0062
Filipina	0.86	0.79	0.93	0.0003
Other Asian/Pacific Islander ethnicity	0.86	0.79	0.93	0.0003
Marital status at diagnosis				
Married (reference)	1.00	-	-	-
Unmarried	1.09	1.06	1.13	<0.0001
Neighborhood socioeconomic status (SES), quintiles				
First (lowest) quintile (reference)	1.00	-	-	-
Second quintile	1.02	0.97	1.08	0.41
Third quintile	0.97	0.92	1.03	0.33
Fourth quintile	0.95	0.89	1.00	0.06
Fifth (highest) quintile	0.87	0.82	0.93	<0.0001
Insurance status				
Private only (reference)	1.00	-	-	-
No insurance	1.20	1.04	1.39	0.013
Medicare with or without private	1.25	1.19	1.32	<0.0001
Any Medicaid, military or other public	1.30	1.24	1.36	<0.0001
Tumor grade				
Grade 1 (reference)	1.00	-	-	-
Grade 2	1.79	1.68	1.90	<0.0001
Grade 3	2.73	2.55	2.91	<0.0001
Tumor histology				

	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Ductal (reference)	1.00	-	-	-
Lobular	1.06	1.00	1.12	0.06
Other	0.73	0.68	0.79	<0.0001
Estrogen/progesterone receptors (ER/PR)				
Either positive (reference)	1.00	-	-	-
Both negative	1.55	1.49	1.61	<0.0001
Lymph node involvement				
Negative (reference)	-	-	-	-
Positive	1.97	1.88	2.06	<0.0001
Reporting hospital National Cancer Institute-designated cancer center				
No (reference)	1.00	-	-	-
Yes	0.89	0.83	0.97	0.005
SES of hospital's patient distribution				
High: ≥50% highest 2 quintiles, <50% lowest 2 (reference)	1.00	-	-	-
Medium: neither low nor high	1.09	1.05	1.13	<0.0001
Low: ≥50% lowest 2 quintiles, <50% highest 2	1.08	1.03	1.14	0.0016
Adjuvant therapy (chemotherapy and/or radiation)				
No (reference)	1.00	-	-	-
Yes	1.12	1.08	1.17	<0.0001

*Fine and Gray regression model with death from another cause as a competing risk, stratified by stage, tumor size and year of diagnosis and adjusted for the variables in the table. N=1,150 with unknown cause of death were excluded.